Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 58-78, 80, 81 and 100 are pending in the application, with claim 58 being the independent claim. Claims 79 and 82-99 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 58-61, 63, 70 and 80 have been amended. These changes are believed to introduce no new matter, and their entry is respectfully requested. Specifically, support for the term "soluble" can be found *inter alia* at page 6, paragraph [0024] of the specification as filed.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Specification

The Examiner stated that the application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). *See* Office Action at page 3. Therefore, Applicants have provided an abstract on a separate sheet of paper on page 8 of this response.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 59-78, 80, 81 and 100 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". *See* Office Action at page 3.

The Examiner first noted that the claims comprise non-elected subject matter. The claims have now been amended such that all pending claims are directed to elected subject matter. Therefore, this rejection is rendered moot.

The Examiner also argued that claim 61 is not clear because there is no comma separating "one or more cysteine residues" and "a purification-facilitating polypeptide." Office Action at page 3. Claim 61 has been amended to include a comma. Therefore, this rejection is rendered moot.

The Examiner further alleged that Claim 63 is indefinite because nucleic acids encode proteins, but whether the protein is cyclic or not is a post-translational event. Office Action at page 3. Applicants respectfully disagree. As disclosed in Example 6 of the application as filed, a cyclic polypeptide can be created by adding cysteines at the N and C termini of the peptide. *See* page 38, lines 15-18 of the specification. Therefore, a nucleic acid encoding a cyclized polypeptide can be created by adding nucleotides encoding cysteines to the termini of the polynucleotide sequence. Thus, Applicants submit that Claim 63 is definite.

Applicants believe they have addressed all of the rejections under 35 U.S.C. 112, second paragraph. As such, Applicants respectfully request reconsideration and withdrawal of these rejections.

Rejections under 35 U.S.C. § 102

Claims 58, 59, 64-66, 69 and 70 are rejected by the Examiner under 35 U.S.C. § 102(b) "as being anticipated by Osada *et al.* (2001; Assignment of 118 novel cDNAs of cynomolgus monkey brain to hum chromosomes. *Gene. 275*: 31-37)" ("Osada"). *See* Office Action at page 4.

According to the Examiner, Osada teaches a nucleic acid encoding LINGO-1 derived from cynomolgus monkey which is a protein sequence that differs from instant SEQ ID NO:2 at Ser527Pro. Office Action at page 4. The protein described by Osada contains a transmembrane domain. Thus, the protein described in Osada would be cell bound and not soluble. In contrast, each of claims 58, 59, 64-66, 69 and 70 as presently amended require that the polypeptide of SEQ ID NO:2 is a *soluble* fragment.

The Examiner further suggested that since cynomolgus monkey LINGO-1 differs from SEQ ID NO:2 at Ser527Pro, Osada teaches LINGO-1 amino acids 1-526 and 528-614 as fragments of SEQ ID NO:2. Office Action at page 4. Applicants respectfully disagree. Osada teaches only the full length cynomolgus monkey LINGO-1 protein. The fact that Applicants have disclosed a sequence which differs from cynomolgus monkey LINGO-1 at amino acid 527 does not indicate that Osada teaches the polypeptide fragment of amino acids 1 to 526. Osada is directed to mapping genes to specific human chromosomes and does not teach or suggest any fragments of LINGO-1. Thus, Osada certainly does not teach or suggest a *soluble* fragment of the polypeptide of SEQ ID NO:2, wherein the polypeptide is capable of decreasing inhibition of axonal growth of a central nervous system neuron.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984). As discussed above, Osada does not expressly or inherently disclose a soluble fragment of SEQ ID NO:2 and therefore does not disclose every element of the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection of the claims as currently amended under 35 U.S.C. § 102(b). In view of the foregoing

remarks, Applicants respectfully assert that Osada does not anticipate claims 58, 59, 64-66, 69 and 70 as amended. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Osada therefore are respectfully requested.

Claims 58-78, 80 and 100 are rejected by the Examiner under 35 U.S.C. § 102(b) "as being anticipated by Jacobs *et al.* (1998; USP 5,707,829)" ("Jacobs"). *See* Office Action at pages 4-6.

Jacobs identified clone L105 from a murine adult thymus library using a trap which selects for nucleotides encoding secreted proteins. L105 encodes the amino acid sequence of SEQ ID NO:6. SEQ ID NO:6 is a 133 amino acid sequence, and amino acids 65-69 of SEQ ID NO:6 correspond to amino acids 454-458 of SEQ ID NO:2 of the present invention, but SEQ ID NO:6 shares no other homology with SEQ ID NO:2. Jacobs teaches that the L105 protein has homology with various monocyte and other chemoattractant proteins and suggests that L105 may share at least some activities with these other proteins. Jacobs at column 5, lines 10-19.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. See *Kalman* 713 F.2d. at 771. The claims of the present invention are directed to a polypeptide which is capable of decreasing inhibition of axonal growth of a central nervous system neuron. Jacobs does not expressly teach this function. Furthermore, the polypeptide described by Jacobs cannot possess this function inherently for the following reasons. The sequence described by Jacobs corresponds to a chemokine (C-C motif) ligand 21a (serine) protein in mouse (NCBI Accession number NP_035254) (Exhibit 1). The murine chemokine (C-C motif) ligand 21a protein, which differs from chemokine (C-C motif) ligand 21a

(serine) only at the single amino acid Ser64Leu, has been further characterized by several other groups including Hedrick *et al.* (*J. of Immunology 159*: 1589-1593 (1997)) ("Hedrick"; Exhibit 2). According to Hedrick, expression of murine chemokine (C-C motif) ligand 21a (called "murine "6Ckine" in the article) was relatively broad in the testis, kidney, liver and heart and was particularly strong in the lung and spleen. *See* page 1590 right column and Figure 2. However, the mRNA was absent in the brain. *Id.* Since the protein is not expressed in the central nervous system, the protein cannot decrease inhibition of axonal growth of a central nervous system neuron. In addition, Hedrick demonstrated that the protein is a member of the chemokine superfamily as was suggested by Jacobs. Chemokines function to regulate cell trafficking, not axonal growth. In addition, chemokines regulate the trafficking of immune system cells, not neuronal cells. Therefore, since the protein described by Jacobs does not explicitly or inherently decrease inhibition of axonal growth, Jacobs does not anticipate the claimed invention.

Jacobs also teaches fragments of the protein of SEQ ID NO:6 which are capable of exhibiting biological activity and further that fragments of the protein may be fused through linker sequences to the Fc portion of an immunoglobulin. Jacobs at column 6, lines 14-26. However, Jacobs does not teach or suggest any polypeptide fragments that are capable of decreasing inhibition of axonal growth of a central nervous system neuron. In fact, Jacobs does not teach any specific fragments of SEQ ID NO:6 at all. Further, as described above, Jacobs does not expressly or inherently teach any polypeptide which is capable of decreasing inhibition of axonal growth of a central nervous system neuron.

Thus, since Jacobs does not teach a polypeptide of SEQ ID NO:2 that is capable of decreasing inhibition of axonal growth of a central nervous system neuron, Jacobs

does not expressly or inherently disclose every element of the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b). In view of the foregoing remarks, Applicants respectfully assert that Jacobs does not anticipate claims 58-78, 80 and 100. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Jacobs therefore are respectfully requested.

Rejections under 35 U.S.C. § 103

I. Rejection over Osada

Claims 58, 69, 70, 71, 72, 80 and 100 are rejected by the Examiner under 35 U.S.C. § 103(a) "as being unpatentable over Osada." *See* Office Action at pages 6-8.

The United States Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The Court stated that the *Graham v. John Deer Co. of Kansas City*, 383 U.S. 1 (1966) factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness (*KSR*, 127 S.Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18)).

The USPTO has recently published guidelines for Examiners in determining whether claims are non-obvious under the KSR holding. 72 FR 57526. In particular, the Office requires that Examiners articulate, in the record, specific findings of fact which, in view of the legal considerations under *Graham*, would render the claimed invention obvious. While the Office sets forth a number of rationales by which a determination of obvious may be made (*id.* at 57529), a common thread throughout requires that the prior

art, in combination with the knowledge ascribed to the person of ordinary skill in the art, provide sufficient information to make the claimed invention fully and easily predictable.

Applicants assert that considering Osada, one of ordinary skill in the art would not have arrived at Applicants' claimed invention with any sort of predictability whatsoever.

A. Scope and Content of the Prior Art

As described above, Osada discloses the cynomolgus monkey LINGO-1 polypeptide. According to Osada, the polypeptide described contains a dihydrogenase/reductase signature, a connexin signature 1, an EGF-like domain signature 2, and a calcium binding EGF signature pattern. *See* Tables 1 and 2. Notably, the polypeptide also contains a transmembrane domain and would therefore be cell bound and not soluble.

B. Differences Between the Prior Art and the Claims

Ascertaining the differences between the claim at issue and the prior art, requires a consideration of both the claimed invention and the prior art as a whole. *See Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479-80 (Fed. Cir. 1998). The appropriate question is not whether the differences themselves would have been obvious, but rather whether the claimed invention as a whole would have been obvious. *See id.* at 1479-1480.

Applicants' invention relates to a soluble fragment of the polypeptide of SEQ ID NO:2 that is capable of decreasing the inhibition of axonal growth of a central nervous system neuron. The teachings of Osada do not teach or suggest Applicants' claimed invention. First, Osada teaches a LINGO-1 polypeptide that comprises a transmembane domain and is not a soluble polypeptide fragment as claimed. Second, Osada does not

even mention a role for the LINGO-1 protein in neurobiology at all and certainly does not indicate that the described polypeptide could be modified in any way to obtain a soluble fragment of the polypeptide that decreases the inhibition of axonal growth of a central nervous system neuron. Upon review of Osada, a person of ordinary skill in the art would not have the motivation or the knowledge of how to make or use the claimed invention.

C. Level of Ordinary Skill in the Pertinent Art

The level of one of ordinary skill in the art, as it relates to the present invention, is that of a neurobiologist or molecular biologist having an M.D. and/or Ph.D. While such a person would certainly possess "ordinary creativity" (KSR, 127 S.Ct. at 1742), the person could not possibly derive the presently claimed invention from Osada with any sort of predictability, without also possessing some level of prescience. This is not the standard under *KSR*.

Taken as a whole, the Examiner has not provided sufficient factual basis for concluding that the claimed invention would have been obvious to a person of ordinary skill in the art. Osada does not even come close to teaching or suggesting all of the limitations of the claimed invention. There is no mention or suggestion of soluble LINGO-1 fragments and no predictable suggestion that any LINGO-1 polypeptides could decrease inhibition of axonal growth.

Thus, for at least these reasons the Examiner has not established a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the rejection of

claims 58, 69, 70, 71, 72, 80 and 100 under 35 U.S.C. § 103(a) over Osada are reconsidered and withdrawn.

II. Rejection over Jacobs

Claims 58-78, 80 and 100 are rejected by the Examiner under 35 U.S.C. § 103(a) "as being unpatentable over Jacobs." *See* Office Action at page 8.

However, Applicants respectfully assert that considering Jacobs, one of ordinary skill in the art would not have arrived at Applicants' claimed invention with any sort of predictability whatsoever.

A. Scope and Content of the Prior Art

As described above, Jacobs teaches the 133 amino acid sequence of L105, which includes the sequence of amino acids 454-458 of SEQ ID NO:2, but shares no other homology with SEQ ID NO:2. The L105 protein is also known as chemokine (C-C motif) ligand 21a (serine) protein, and chemokines function to regulate the trafficking of immune cells. In addition, Hedrick demonstrated that chemokine (C-C) motif ligand 21a protein is expressed in testes, kidney, liver, heart, lung, and spleen, but was not expressed in the brain.

B. Differences Between the Prior Art and the Claims

As described above, Applicants' invention relates to a soluble fragment of the polypeptide of SEQ ID NO:2 that is capable of decreasing the inhibition of axonal growth of a central nervous system neuron. The teachings of Jacobs do not teach or suggest Applicants' claimed invention. The protein described by Jacobs regulates immune cells, and Jacobs does not even hint that the protein has any neuronal function. In fact, Hedrick teaches that chemokine (C-C) motif ligand 21a is not even expressed in

the brain, and therefore teaches away from use as a regulator of axonal growth of a central nervous system neuron. Therefore, Jacobs does not teach or suggest a soluble fragment of the polypeptide of SEQ ID NO:2 that is capable of decreasing inhibition of axonal growth of a central nervous system neuron.

C. Level of Ordinary Skill in the Pertinent Art

As described above, the level of one of ordinary skill in the art, as it relates to the present invention, is that of a neurobiologist or molecular biologist having an M.D. and/or Ph.D. However, the Examiner has not provided sufficient factual basis for concluding that the claimed invention would have been obvious to a person of ordinary skill in the art. Since Jacobs does not even remotely suggest that L105 has a neuronal function, one of skill in the art would certainly not have the knowledge or motivation to modify the teachings of Jacobs to obtain the claimed invention. Furthermore, even if one of skill in the art were motivated to modify the polypeptide described by Jacobs, Jacobs teaches a 133 amino acid protein sequence and does not particularly identify the specific amino acid sequence that corresponds to amino acids 454-458 of SEQ ID NO:2. Therefore, one of skill in the art would have not have any suggestion to modify the protein described by Jacobs using the claimed region or to obtain the claimed function.

Thus, for at least these reasons the Examiner has not established a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the rejection of claims 58-78, 80 and 100 under 35 U.S.C. § 103(a) over Jacobs are reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Cynthia L. DeRenzo

Cynthia L. DeRenzo
Agent for Applicants
Registration No. 60,789

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
931675_3.DOC